Original Article

Realisation of Remission of Diabetes Using Pharmacotherapy (DiaRem-1)

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Abstract

Introduction: Type 2 diabetes mellitus has traditionally been considered a lifelong disease, with treatment focused on glycaemic control and complication prevention. Emerging evidence suggests that targeting glucolipotoxicity and insulin resistance may restore beta-cell function, potentially leading to remission. This study aimed to evaluate the feasibility of achieving diabetes remission through pharmacotherapy by promoting weight loss and maintaining strict glycaemic control over a 3-month period. **Methods:** This is a single-centre, open-label, randomised controlled trial conducted at a tertiary care center in India, with adult subjects with type 2 diabetes mellitus <5 years duration and HbA1c <8.5% randomised to an intervention arm using liraglutide, dapagliflozin and metformin, and a control arm using vildagliptin, glimepiride and metformin. The subjects were treated for 3 months followed by an off-treatment period for 3 months to assess for remission of diabetes. **Results:** Two hundred thirty-six subjects were assessed for eligibility and 29 subjects underwent randomisation. Fourteen subjects were randomised to the intervention arm and 15 subjects were randomised to the control arm. Twenty-three of the 29 recruited subjects completed the trial. At the end of the off-treatment period, nine patients (31.04%) were in remission, with 4 out of 14 patients (28.57%) in the intervention arm and 5 out of 15 patients (33.33%) in the control arm maintaining HbA1c less than 6.5% without any treatment. No baseline clinical or biochemical parameters were found to be reliable predictors of remission. **Conclusion:** This trial provides evidence that pharmacotherapy targeting tight glycaemic control on an outpatient basis is effective in achieving diabetes remission.

Keywords: Dapagliflozin, diabetes, liraglutide, pharmacotherapy, remission, vildagliptin

Introduction

Type 2 diabetes mellitus has long been a lifelong disease with treatment aimed at controlling the disease and preventing complications. The treatment of this morbid condition has evolved overtime. Now the question is, can the disease be cured? Ongoing glucotoxicity and lipotoxicity have been proposed to be culprits behind the deterioration in beta cell function. Hence any attempt to cure diabetes should aim to return beta cell function to its baseline by targeting glucolipotoxicity. Furthermore, it has previously been demonstrated that in the years preceding the onset of diabetes, insulin resistance remains constant but beta cell function rapidly deteriorates.[1] With increasing duration of diabetes, beta cell function further deteriorates. Therefore, targeting glucolipotoxicity along with insulin resistance may bring diabetes into remission. At present, weight loss programmes and metabolic surgery have shown to induce prolonged remission of diabetes. However, these methods are not applicable on a widescale, and are fraught with long term compliance issues, expenditure and associated potential complications. Insulin resistance can be lowered with weight loss, while alleviating glucolipotoxicity requires attaining normoglycaemia even below the pre-diabetic range. However, the limited pharmacological options and their associated hypoglycaemic potential had made attainment of normoglycaemia a distant dream in the past. With the advent of newer agents having negligible risk for hypoglycaemia, achieving a near normal glycaemia has become a feasible target. In this trial, we assessed efficacy and safety of a combination pharmacotherapy to achieve normoglycaemia, followed by withdrawal of the therapy to look for persistent remission of T2DM.

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Materials and Methods

This study was conducted in a tertiary care institute in India. All consecutive patients with T2D were recruited following fulfilment of the following inclusion and exclusion criteria: duration of diabetes less than 5 years with an HbA1c less than 8.5% and not on insulin therapy, and no major comorbidities. They were advised lifestyle and dietary modifications, along with statin therapy and blood pressure control as indicated. Subjects were advised to follow active lifestyle with at least 150 min/wk of moderate intensity physical activity. All subjects were given a personalised diet chart targeting a caloric deficit of 500 kcal/day. During run in period, all antidiabetic medications were withheld and they were placed on metformin monotherapy at doses of 1000-2000 mg/day. After 2 weeks of metformin monotherapy, all subjects underwent mixed meal tolerance test, anthropometric measurements and body composition estimation (assessed by single-frequency bioelectrical impedance analysis device (Omron HBF-302, Kyoto, Japan)). Mixed meal (500 kcal, Ensure, Abbott Nutrition, Abbott Laboratories, India) dissolved in 500 mL of water was administered to the subjects, to be taken within 10 min. Samples for insulin and glucose were collected at 0, 30, 60, 90 and 120 min. They were then randomised into two groups using block randomisation stratified based on duration of diabetes (less than 2 years and more than 2 years). In group A (intervention arm) the subjects were started on tablet dapagliflozin 5 mg once daily (with dose increased to 10 mg once daily after one week if tolerated) and injection Liraglutide 0.6 mg subcutaneous once daily, with dose up titrated every week by 0.6 mg depending on tolerability, to a maximum dose of 3 mg weekly (1.8 mg weekly if BMI <27 kg/m^2). Metformin was continued at maximal tolerated doses up to 2000 mg/day. In Group B (control arm), the subjects were continued on metformin at maximum tolerated doses. Based on glycaemic control vildagliptin at a dose of 100 mg/day and glimepiride at a dose of 1-4 mg/day were sequentially added. Dose titration was then done on a weekly basis based on plasma glucose levels during follow-up. They were not started on SGLT-2 inhibitors, GLP-1 receptor agonists or insulin. Monitoring and titration was done every week. A convenient sample size of 56 was initially planned, but due to the impact of the COVID-19 pandemic, the study ultimately included a total of 29 patients.

In both the groups, blood glucose was monitored weekly and doses of drugs were titrated to maintain fasting blood glucose less than 100 mg/dL, postprandial blood glucose <140 mg/dL and avoiding any random glucose value <70 mg/dL. In group A, doses of the medications were titrated to maximum tolerated doses even if glycaemic targets have been achieved with lower doses. This was done to maximise weight loss. In group B, vildagliptin and glimepiride were added sequentially to achieve target glycaemia. All subjects were explained about the signs and symptoms of hypoglycaemia. In both the groups, once glycaemic targets were achieved, the therapy was continued for another 3 months (*active treatment period*). At the end of 3 months, all drugs were stopped and the patients were followed up without treatment for another 3 months (*off-treatment period*) to look for remission of diabetes. Remission of diabetes was defined as per the recent consensus of maintaining HbA1c less than 6.5% without any antidiabetic therapy for 3 months.[2] All patients underwent repeat mixed meal tolerance test, anthropometric measurements, and body composition estimation after 2 weeks of stopping treatment. Following drug discontinuation, the subjects were followed up telephonically weekly for next 3 months with fasting blood glucose. If the fasting blood glucose was more than 126 mg/dL on two consecutive occasions, metformin was restarted followed by addition of other antidiabetic medications if required. Repeat HbA1c measurement was done at 3 months after the end of the *off-treatment period*. The patients were advised to continue diet and lifestyle modifications throughout the entire study period.

Selected patients in the intervention arm underwent MRI abdomen to look for change in visceral fat with treatment. Chemical shift MRI was done on a 1.5 Tesla scanner (Siemens, Magnetom plus, Siemens Medical Systems, Erlangen, Germany).

Statistical analysis

Normality of quantitative data was assessed using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± SD and range, with group comparisons using the Student's *t*-test. Skewed data were shown as median (IQR) and compared using the Mann-Whitney U test. Categorical variables were reported as counts and percentages, analysed using the Chi-square test (if all expected cell frequencies >5) or Fisher's Exact test (if <5). ROC curves determined optimal cut-off values, plotting sensitivity vs. 1-specificity. Significant factors from bivariate analysis were included in logistic regression to calculate odds ratios for remission. $P < .05$ was significant. Analysis was performed using IBM SPSS (version 22.0).

Ethical aspect

The study was approved by the Institute Ethics Committee of PGIMER, Chandigarh (Approval No INT/IEC/2021/SPL-1183 dated 4/8/2021). All participants provided written informed consent before enrolment.

Results

Baseline characteristics

Two hundred thirty-six patients were assessed for eligibility and 29 underwent randomisation [Figure 1]. The baseline characteristics were evenly matched in both groups [Table 1]. Patients in the intervention arm had a median age of 51 years and a median (IQR) duration of 18 (9.5-32.75) months, while those in the control arm had a median age of 40 years and a median duration of diabetes of 14 (10-29) months. The mean baseline weight in the intervention arm was 76.85 (±17.14), and BMI was 29.20 (±4.74). The mean

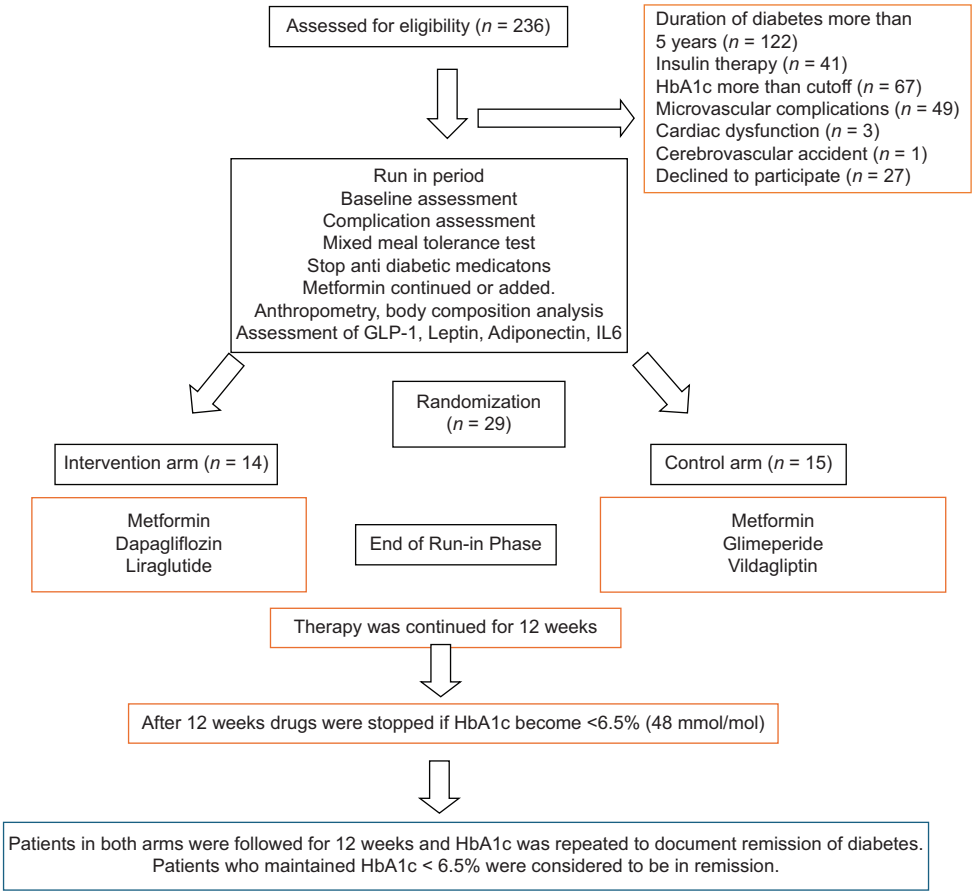

Figure 1: Flow diagram of the trial design

Table 1: Baseline characteristics

Variable	Intervention arm (*n*=14)	Control arm (*n*=15)	*P*
Age (years)	51 (40-58)	40 (37-51)	0.10
Female sex	8 (61.5%)	5 (38.5%)	0.20
Duration of diabetes (months)	20.5±12.45	18.67±13.31	0.71
Hypertension	1 (7.1%)	3 (20%)	0.32
Hypothyroidism	2 (14.3%)	3 (20%)	0.68
Smoking	2 (14.3%)	2 (13.3%)	0.94
Alcohol	6 (42.9%)	5 (33.3%)	0.60
Weight (kg)	75 (68-82.95)	81.6 (64.4-85.5)	0.51
BMI (kg/m^2)	28.5 (25.6-32.4)	26.78 (25.46-32.05)	0.72
HbA1c (%)	6.39±0.39	6.75±0.79	0.14
No. patients on medications	12 (92.31%)	11 (73.3%)	0.59
No. patients on >1 antidiabetic agents	6 (46.15%)	7 (46.66%)	0.64
HOMA-IR	3.25 (2.42-4.21)	3.13 (1.96-4.12)	0.91
Fasting insulin (µIU/ml)	13.25 (9.76-15.43)	12.10 (7.72-16)	0.23
Fasting C-peptide (ng/ml)	2.9 (2.62-3.22)	2.96 (2.23-3.59)	0.36
Peak stimulated C-peptide (ng/ml)	11.85 (9.41-14)	10.7 (8.18-13.01)	0.72
Disposition index	1.96 (0.9-4.81)	1.98 (0.26-4.89)	0.996

baseline weight in the control arm was 78.72 (±14.75) and BMI was 29.18 (±6.13) kg/m^2. Hba1c at the time of diagnosis was not available for two subjects in the control arm and three subjects in the intervention arm. In the remaining subjects, the median HbA1c was 7.7 (6.9-8.1) in the intervention arm and 8.5 (7.1-9.25) in the control arm. Twenty-three patients were on oral antidiabetic agents prior to the start of the trial with 44.83% of subjects being on more than one drug. HbA1c at the time of enrolment and randomisation to the trial was similar in both the groups with a median HbA1c of

6.35 (6.20-6.63) in the intervention arm and 6.5 (6.1-7.4) in the control arm.

Primary outcome

Twenty-three of the 29 recruited subjects completed 3 months of *active-treatment period* and following that all the antidiabetic medications were stopped. They were followed up for a further 3 months after stopping treatment (*off-treatment period*). At the end of the *off-treatment period*, 9 patients (31.04%) were in remission, with 4 out of 14 patients (28.57%) in the intervention arm and 5 out of 15 patients (33.33%) in the control arm maintaining HbA1c less than 6.5%.

Changes in parameters at the end of the active-treatment period

Both groups achieved significant weight loss: median (IQR) -4.9 (-2.9 to -8.68) kg in the intervention arm and -3 (-6.40 to + 0.7) kg in controls (P = .14). All intervention subjects lost weight, while three in the control arm gained weight. Maximum weight loss was 12.9 kg (intervention) and 9.4 kg (control). Both groups had significant fat mass (-3.2 kg vs -3.8 kg) and body fat percentage (-2.75% vs -3.10%) reductions [Tables 2 and 3]. After 3 months, mean (SD) HbA1c was 5.96 (0.35) vs 5.95 (0.39). Median (IQR) HOMA-IR change was -0.32 (-2.18 to + 0.54) vs -0.44 (-2.11 to + 1.12), and median disposition index increase was 0.36 vs 0.77, both non-significant. During off-treatment, subjects were followed up for glycaemic monitoring. Nineteen required metformin for fasting glucose >126 mg/dL, while ten completed without medication. Nine had HbA1c <6.5%, indicating remission.

Predictors of remission

Baseline characteristics did not differ significantly. Those in remission had a shorter median diabetes duration (12 vs 23.5 months, max 36 months) and greater weight loss (4.7% vs 3%, P = n.s.) [Table 4]. One control subject achieved remission despite gaining 0.7 kg. At the end of treatment, the disposition index was significantly higher in those achieving remission [mean (SD) 5.25 (±2.85) vs 2.04 (±0.91)], with a significantly greater increase [1.75 (0.26 to 4.20) vs -0.04 (-1.14 to + 0.79)]. Post-treatment HOMA-IR was also significantly lower in the remission group [2.09±0.83 vs 3.72 ± 1.59; P = 0.01].

Eight patients in the intervention arm underwent an MRI abdomen prior to the initiation of treatment. Six patients underwent repeat imaging after treatment, while 2 patients did not consent for the same. Four of them had a significant degree of hepatic steatosis prior to treatment and three of them had pancreatic fat more than 5%. In these subjects, the median relative reduction in liver fat was 51.3% and the median relative reduction in pancreatic fat was 48.2%.

Adverse events

Gastrointestinal symptoms (dyspepsia, bloating, nausea, diarrhoea) were common, affecting 72.73% in the intervention arm vs. 15.39% in controls, but were transient and required no treatment changes. Liraglutide's maximum dose was tolerated by 55%. One intervention patient developed stomatitis, which resolved spontaneously. A male on dapagliflozin had balanitis, resolving after a one-week drug pause, with no relapse upon reintroduction. Hypoglycaemia was absent in the intervention arm but occurred in two control patients (one level 1, one level 2). One control patient developed generalised itching, which resolved after stopping vildagliptin.

Table 2: Change in parameters with treatment

Parameters	Intervention arm	*P*	Control arm	*P*
Weight loss (kg)	4.7 (2.6-6.65)	0.001	3 (-0.7 - +6.4)	0.02
Change in BMI (kg/m^2)	-1.58 (-0.89- -2.8)	0.002	-1.10 (-2.82- -0.12)	0.03
Body fat% reduction	2.75 (0.5-3.55)	0.018	3.10 (0.1-5.9)	0.003
Fat mass reduction (kg)	-3.2 (-1.15 - -4.3)	0.01	-3.8 (-6.7- +0.3)	0.01
ΔHOMA-IR	-1.79 (-2.45- +2.44)	0.387	-0.44 (-2.11- +1.12)	0.53
ΔDisposition index	0.74 (-0.02- +3.58)	0.446	0.77 (-0.26- +1.75)	0.15

Table 3: Comparison of treatment related changes

Parameters	Intervention arm	Control arm	*P*
Weight loss (kg)	4.7 (2.6-6.65)	3 (-0.7- +6.4)	0.25
Change in BMI (kg/m^2)	-1.58 (-0.89- -2.8)	-1.10 (-2.82- -0.12)	0.33
Body fat% reduction	2.75 (0.5-3.55)	3.10 (0.1-5.9)	0.74
Fat mass reduction (kg)	-3.2 (-1.15- -4.3)	-3.8 (-6.7 - +0.3)	0.96
ΔHOMA-IR	-1.79 (-2.45- +2.44)	-0.44 (-2.11 - +1.12)	0.95
ΔDisposition index	0.74 (-0.02- +3.58)	0.77 (-0.26- +1.75)	0.72
Peak stimulated C-peptide after treatment (ng/ml)	10.15 (5.72-20.8)	8.78 (5.84-21)	0.87
ΔStimulated C-peptide	-1.18 (-5.11- +5.20)	-0.29 (-7.26- +6.00)	0.70
Post treatment HbA1c (%)	5.96±0.35	5.95±0.39	0.97

Table 4: Predictors of remission

Variable	Remission group	Non-remission group	*P*
Age (years)	40 (37-52)	42.5 (39-55)	0.53
Duration of diabetes (months)	12 (3.5-30.5)	23.5 (12-33)	0.16
Baseline weight (kg)	72.5 (61.9-86.25)	78.5 (67.17-86.03)	0.59
Baseline BMI (kg/m^2)	-1.2 (-0.68- -3.3)	-1.1 (-0.3- -2.7)	0.62
Weight loss (%)	4.7 (2.6-8)	3 (0.9-5.4)	0.33
Change in BMI (kg/m^2)	-1.2 (-0.68- -3.3)	-1.1 (-0.3- -2.7)	0.62
Baseline HbA1c (%)	6.5 (6.35-6.75)	6.35 (6.05-6.68)	0.86
Baseline HOMA-IR	3.76 (2.47-4.03)	2.93 (2.36-4.25)	0.63
Fasting C-peptide (ng/ml)	2.96±0.85	3.05±0.62	0.82
Baseline stimulated C-peptide (ng/ml)	9.71 (7.7-12.9)	11.3 (7.92-14.1)	0.78
Baseline disposition index	2.45 (1.60-4.57)	1.74 (0.83-2.52)	0.97
Post-treatment stimulated C-peptide (ng/ml)	6.93 (5.84-12.30)	10.34 (5.72-21)	0.19
Post treatment HbA1c (%)	6±0.3	6.12±0.32	0.39
Post-treatment HOMA-IR	1.91 (1.1-2.58)	3.33 (2.35-5.29)	0.03
Post-treatment disposition index	6.84 (4.74-9.46)	1.76 (1.13-2.70)	0.002
ΔHOMA-IR	-1.97 (-0.34- -2.43)	-0.36 (-2.21- +0.51)	0.46
ΔDisposition index	3.58 (2.13-6.3)	0.03 (-0.94- +0.79)	0.002

Discussion

Persistent hyperglycaemia suppresses insulin production and secretion, and promotes beta cell apoptosis without increasing compensatory beta cell regeneration.[3] A positive caloric balance increases circulating free fatty acid levels which lead to oxidative stress in beta cells in addition to worsening peripheral resistance.[4] In this trial, we used pharmacotherapy that is widely employed in the treatment of diabetes but altered the glycaemic targets so as to maintain tight glycaemic control in the quest to achieve remission of diabetes. Nearly one-third of the study subjects achieved remission. This is in concordance with the previously reported rates of remission achieved with intensive lifestyle intervention and dietary interventions, which are more difficult to comply with as it involves liquid diets/meal replacements. In an ancillary study of the LOOK AHEAD trial, Gregg *et al*.[5] assessed the remission rates achieved with intensive lifestyle intervention (ILI). The LOOK AHEAD trial was originally designed to assess the cardiovascular benefits of weight loss programmes. The patients were randomised to either an intensive lifestyle intervention group or to receive diabetes support and education. ILI aimed at maintaining a calorie intake of 1200-1800 kcal/d and increasing physical activity to at least 175 min/wk. Mean weight loss was 8.6% in these study subjects. The ILI group experienced significantly higher remission compared to the control group at 1 year (11.5% vs 2%) and at 4 years (7.3% vs 2%). The DiRECT trial compared a weight loss programme with guideline-based standard diabetes care in obese patients diagnosed with T2D in the past 6 years.[6] The intervention arm received 825-853 kcal formula diet per day for 12 weeks, followed by a 6-week transition phase and maintenance on weight loss diet to a total of 104 weeks. 46% of patients in the intervention group achieved HbA1c <6.5% compared to 4% in the control group. The remission rates were higher with greater degree of weight loss.

In our study, there was no difference in the rates of remission between the intervention group and control group. This possibly happened due to near equal amelioration of glucotoxicity in both the groups, as post-treatment HbA1c was similar in both the groups. Both treatment modalities resulted in significant reduction in weight, BMI, body fat mass and fat percentage with no between-group differences in the above parameters, though weight loss tended to be higher in the intervention group. The near-equal weight loss in both groups reflects the compliance of the subjects to the lifestyle and dietary modifications that were advised. Indices of insulin resistance (HOMA-IR) and beta cell function (disposition index) did not show any significant change in either group.

How to identify subjects who are likely to achieve remission? Younger age, shorter duration of diabetes, higher baseline beta cell function and better baseline glycaemic control have been described as predictors of remission in some, but not all, studies.[7] In our present study, none of these factors were found to predict remission reliably. However, our trial excluded patients with a duration of T2D of more than 5 years and those who had poor glycaemic control as evidenced by an HbA1c of more than 8.5% or requiring insulin therapy. No baseline parameters were found to be reliable predictors of remission. This finding is reassuring in that all patients with T2D should be seen as potential candidates for remission-directed treatment and broadens the applicability of the study findings.

Findings at the end of the *active treatment period* were analysed to determine if any factors could predict remission after 3 months of follow-up without any antidiabetic therapy. Although significant weight loss was achieved with treatment, no degree of weight loss could predict the persistence of remission at 3 months of follow-up after stopping treatment. This is in contrast to earlier findings where weight loss achieved with intervention has been consistently shown to

predict remission. 10-15 kg weight loss has been proposed to lead to remission in newly diagnosed T2D undergoing bariatric surgery.[8-10] In the DiRECT trial, the incidence of remission was categorised depending on the degree of weight loss achieved: 5% of those who lost less than 5 kg, 29% of those who achieved 5 kg to less than 10 kg weight loss, 60% of those who achieved 10 kg to less than 15 kg weight loss, and 70% participants who lost 15 kg or more achieved remission.[11] The mean weight loss in this trial was 10 kg. In our present study, there was a tendency for greater weight loss in the patients who maintained remission compared to those who relapsed although it did not reach statistical significance. The median weight loss in the responder cohort was 4.7 kg compared to 3 kg in the group who relapsed. Only two patients achieved a weight loss of more than 10 kg in the study cohort. The relatively short duration of the study may have limited the degree of weight loss. Despite the major weight loss, one-third of our study subjects were able to achieve remission, probably as we were able to achieve near-normal glycaemia in these subjects and hence alleviate glucotoxicity.

Beta cell function at the end of the *active treatment period* as assessed by oral disposition index showed significant improvement in those patients who maintained remission. This is in line with current evidence that although weight loss and improvement in insulin sensitivity is necessary for achieving remission, ultimately it is the degree of recovery of beta cell function that determines whether remission will be sustained.[12] Recent studies have shown that weight loss can induce re-differentiation of those β-cells that had undergone de-differentiation in the presence of metabolic stress.[13] The recovery of beta cells diminishes as the duration of diabetes increases.[14]

Lower HOMA-IR at the end of the *active treatment period* was predictive of remission. The HOMA-IR at the end of treatment showed a negative correlation with a reduction in fat mass and percentage, emphasising the necessity for weight reduction in achieving remission.

The reduction of liver fat in MRI did not correlate with the degree of weight loss or reduction in total body fat. Dapagliflozin has been shown to reduce hepatic triglyceride content by differential inhibition of lipogenetic enzymes and by restoring autophagy.[15] Dapagliflozin in combination with omega-3 fatty acids and DPP-4 inhibitors has been shown to reduce hepatic fat content as assessed by MRI-PDFF.[16,17] Similarly, liraglutide has been shown to reduce hepatic fat content.[18] However, in these studies, the reduction in visceral fat content correlated with the degree of weight loss.

Strength and limitations of the study

This is the first study realising remission of diabetes mellitus using pharmacotherapy. Limitations of the study were that it was a single-centre trial, with a relatively small sample size. The duration of treatment was 3 months; hence, further studies with larger sample sizes and longer duration of treatment may be required to further validate the results.

Conclusion

Pharmacotherapy along with lifestyle modification targeting tight glycaemic control and weight loss on an outpatient basis is an effective modality in achieving remission of diabetes.

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Authors' contribution

R.W conceptualized and designed the study, recruited, counselled and managed the patients, collected and interpreted the data and edited the manuscript. A.S recruited and managed the patients, conducted anthropometric measurements and stimulation tests, collected and interpreted the data, and edited the manuscript. S.B was involved in acquisition and interpretation of the data of stimulation tests. D.A helped in editing the manuscript. H.B was involved in the acquisition of MRI abdomen and calculation of visceral fat content. S.K.B was involved in recruitment of patients and interpretation of data. S.M was responsible for dietary planning and counselling of the study subjects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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